

We claim:

1. A transgenic non-human mammal whose genome comprises a transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous amyloid precursor protein 695 (APP₆₉₅) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and wherein the transgene is expressed.
2. The transgenic mammal of claim 1 wherein the mammal is a mouse.
3. The transgenic mouse of claim 2 wherein the mouse is a (C3H x C57 BL6) x C57 mouse.
4. The transgenic mouse of claim 3 wherein the heterologous APP₆₉₅ is human APP₆₉₅.
5. The transgenic mouse of claim 4 wherein the mouse displays abnormal A β deposition in its central nervous system.
6. The transgenic mouse of claim 4 wherein the animal displays an accelerated appearance of Alzheimer's Disease-related pathology.
7. A transgenic mouse having the transgenic mouse of claim 4 as an ancestor.
8. A transgenic non-human mammal produced by:

(a) crossing a first transgenic non-human mammal in accordance with claim 1 with a second non-human mammal having a genome comprising a second gene comprising a nucleotide sequence operably linked to a promoter and encoding a selected protein having at least one selected mutation to produce first generation offspring; and

(b) selecting from the first generation offspring a transgenic non-human mammal having a genome comprising at least one first transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous APP₆₉₅ polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and at least one second gene comprising a nucleotide sequence operably linked to a promoter and encoding said selected protein having at least one selected mutation and expressing both said at least one first transgene and said at least one second gene.

9. The transgenic non-human mammal of claim 8 wherein the selected protein is a presenilin and the selected mutation is an AD-related mutation.

10. The transgenic non-human mammal of claim 8 wherein the selected protein is selected from the group consisting of a low density lipoprotein receptor related gene, an α 2-macroglobulin gene and a β -secretase gene and the selected mutation is an A β processing-related mutation.

11. The transgenic non-human mammal of claim 10 wherein the mammal is a mouse.

12. A transgenic mouse produced by:

- (a) crossing a first transgenic mouse in accordance with claim 4 with a second mouse having a genome comprising a second gene comprising a nucleotide sequence operably linked to a promoter and encoding a selected protein having at least one selected mutation to produce first generation
5 offspring; and
- (b) selecting from the first generation offspring a transgenic mouse having a genome comprising at least one first transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous APP₆₉₅ polypeptide wherein the lysine residue at position 670 is substituted by
10 asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and at least one second gene comprising a nucleotide sequence operably linked to a promoter and encoding said selected protein having at least one selected mutation and expressing both said at least one first transgene and said at least
15 one second gene.
13. The transgenic mouse of claim 12 wherein the second gene is a mutant endogenous gene.
- 20 14. The transgenic mouse of claim 12 wherein the second gene is a transgene.
15. The transgenic mouse of claim 12 wherein the second gene comprises a nucleotide sequence encoding a selected protein having an AD-related amino
25 acid substitution.
16. The transgenic mouse of claim 15 wherein the selected protein is a presenilin.

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17. The transgenic mouse of claim 12 produced by:

(a) crossing a first transgenic mouse in accordance with claim 4 with a second transgenic mouse having a genome comprising a transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous presenilin 2 polypeptide wherein the methionine residue at position 239 is substituted by valine to produce first generation offspring; and

(b) selecting from the first generation offspring a transgenic mouse having a genome comprising at least one first transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous amyloid precursor protein (APP) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and at least one second transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous presenilin 2 polypeptide wherein the methionine residue at position 239 is substituted by valine and expressing both said first and second transgenes.

18. The transgenic mouse of claim 12 produced by:

(a) crossing a first transgenic mouse in accordance with claim 4 with a second transgenic mouse having a genome comprising a transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous presenilin 1 polypeptide wherein the leucine residue at position 286 is substituted by valine to produce first generation offspring; and

(b) selecting from the first generation offspring a transgenic mouse having a genome comprising at least one first transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous amyloid precursor protein (APP) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by

phenylalanine and at least one second transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous presenilin 1 polypeptide wherein the leucine residue at position 286 is substituted by valine and expressing both said first and second transgenes.

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19. The transgenic mouse of claim 12 produced by:

- (a) crossing a first transgenic mouse in accordance with claim 4 with a second transgenic mouse having a genome comprising a transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous presenilin 1 polypeptide wherein the methionine residue at position 146 is substituted by leucine and the leucine residue at position 286 is substituted by valine to produce first generation offspring; and
- (b) selecting from the first generation offspring a transgenic mouse having a genome comprising at least one first transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous amyloid precursor protein (APP) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and at least one second transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous presenilin 1 polypeptide wherein the methionine residue at position 146 is substituted by leucine and the leucine residue at position 286 is substituted by valine and expressing both said first and second transgenes.

20. A method for screening a candidate compound for its efficacy in preventing or delaying the development of AD, the method comprising the steps of:

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(a) administering the candidate compound to a first transgenic mouse in accordance with any one of claims 1 to 19 prior to the appearance of a selected AD-related phenotypic trait in said mouse; and

(b) comparing the age at which said selected AD-related phenotypic
5 trait appears in said mouse with the age at which said trait appears in a second transgenic mouse of the same type to which the compound had not been administered;

wherein an increased age of appearance of the trait in the first mouse compared to that in the second mouse indicates efficacy of the compound.

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✓ 21. The method of claim 20 wherein the trait is a behavioural deficit.

✓

22. The method of claim 20 wherein the trait is abnormal CNS amyloid deposition.

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✓ 23. A method for screening a candidate compound for its efficacy in ameliorating the symptoms of Alzheimer's Disease, the method comprising the steps of:

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(a) administering the candidate compound to a first transgenic mouse in accordance with any one of claims 1 to 19;

(b) determining the performance of said mouse in a memory or learning test; and

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(c) comparing the performance of said mouse with the performance of a second transgenic mouse of the same type to which the compound has not been administered;

wherein an improved performance of the first mouse compared to that of the second mouse indicates efficacy of the compound.

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24. A method of producing a transgenic non-human mammal that displays abnormal A β deposition in its central nervous system comprising:

- (a) introducing into a fertilized oocyte of said mammal a transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous amyloid precursor protein 695 (APP₆₉₅) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine;
- (b) transplanting said fertilized oocyte into a pseudopregnant mammal;
- (c) allowing said fertilized oocyte to develop into a live born offspring; and
- (d) selecting an offspring where genome comprises a transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous amyloid precursor protein 695 (APP₆₉₅) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and wherein the transgene is expressed.

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25. The method of claim 24 wherein the mammal is a mouse.

26. The method of claim 24 wherein the promoter is the prion protein cos.Tet promoter.

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27. A nucleotide sequence encoding a heterologous amyloid precursor protein 695 (APP₆₉₅) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted

by leucine and the valine residue at position 717 is substituted by phenylalanine.

28. A vector comprising the nucleotide sequence of claim 27 operably
5 linked to a promoter.

29. A method of reducing a cognitive deficit in a mammal which suffers
from abnormal amyloid deposition in its central nervous system, the method
comprising administering to the mammal an amount of an A β peptide effective
10 to reduce the cognitive defect.

30. The method of claim 29 wherein the abnormal amyloid deposition is A β
deposition.

15 31. The method of claim 29 wherein the administered peptide is A β 42.

32. The method of claim 29 wherein the mammal is a human suffering from
Alzheimer's Disease.

20 33. Use of an A β peptide to manufacture a medicament for reducing a
cognitive deficit in a mammal which suffers from abnormal amyloid deposition
in its nervous system.

34. The use of claim 33 wherein the A β peptide is A β 42.

25 35. The use of claim 33 wherein the medicament is for the prevention or
treatment of Alzheimer's Disease.

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